the expression of the gene is regulated in a tissue specific manner by the cis-acting regulatory and promoter elements.

The vectors of the invention may be used to deliver and express a mammalian wildtype gene in vivo or ex vivo in a tissue specific manner for both therapeutic and research purposes. The recombinant adeno-associated virus vectors of the present invention may also be used to deliver and express a mammalian gene for research and diagnostic approaches in vitro cell culture systems.

Prior to the present invention, much work was focused on the generation of recombinant adeno-associated viral vectors capable of achieving high levels of expression of a heterologous gene which may have some utility in gene therapy protocols. An abstract published by the inventor's own research group, describes such a vector which was used in an in vitro study to demonstrate the effective transfer of a mutant globin gene to the genome of a erythroleukemia cell in cell culture (Welsh *et al.*, 1991, Clinic. Research 39(2):325A [U]). However, it the present invention that demonstrates for the first time an adeno-associated virus engineered to express a wildtype gene under the control of cis-acting regulatory elements which is capable of transducing a target mammalian host cell, integrate the host cell genome and stably express the wildtype gene in vivo for a prolonged period of time, thus effecting a change in the phenotype of the host cell.

The Examiner's attention is invited to the Rule 132

Declaration of Dr. Richard Jude Samulski submitted on August 13, 1998 in the present application. As described in the Samulski Declaration, experiments were conducted in which blood derived cells were isolated, transduced using recombinant adeno-associated virus vectors expressing a wildtype neomycin resistance gene, and transferred back into a γ-irradiated primate host. As indicated by the data presented in the Samulski Declaration, the transferred wildtype transgene could be detected in the peripheral blood mononuclear cells (PB) and bone marrow (BM) from three of the six experimental animals (See ¶6, Samulski Declaration). Further, in one experimental animal the transgene could be detected for up to three months following transduction.

Thus, the Samulski Declaration demonstrates the successful application of the vectors of the instant invention to achieve detectable expression of the introduced wildtype gene to achieve phenotypic change in vivo. The data presented in the Samulski declaration demonstrates the unexpected and surprising benefits of the present invention. This data is sufficient to rebut even a prima facie case of obviousness. Thus, assuming arguendo that the Examiner may establish a prima facie case of obviousness with the references previously cited, Applicants may point to unexpected or surprising results in order to rebut the same and demonstrate non-obviousness. See In Re Chupp, 816 F.2d 643, 2 USPQ 2d 1437 (Fed. Cir. 1987).

CONCLUSION

Entry of the foregoing remarks into the file of the above-identified application is respectfully requested. Applicants believe that the invention defined by the claims meets all the requirements for patentability. Withdrawal of all rejections and reconsideration of the amended claims so requested. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosure